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REDD1 integrates hypoxia-mediated survival signaling downstream of phosphatidylinositol 3-kinase.

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Cancer cells frequently evade apoptosis during tumorigenesis by acquiring mutations in apoptotic regulators. Chronic activation of the PI 3-kinase-Akt pathway through loss of the tumor suppressor PTEN is one mechanism by which these cells can gain increased protection against apoptosis. We report here that REDD1 (RTP801) can act as a transcriptional downstream target of PI 3-kinase signaling in human prostate cancer cells (PC-3). REDD1 expression is markedly reduced in PC-3 cells treated with LY294002 (LY) or Rapamycin and strongly induced under hypoxic conditions in a hypoxia-inducible factor-1 (HIF-1)-dependent manner. Loss of function studies employing antisense molecules or RNA interference indicate that REDD1 is essential for invasive growth of prostate cancer cells in vitro and in vivo. Reduced REDD1 levels can sensitize cells towards apoptosis, whereas elevated levels of REDD1 induced by hypoxia or overexpression desensitize cells to apoptotic stimuli. Taken together our data designate REDD1 as a novel target for therapeutic intervention in prostate cancer.

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